

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Prevalence of Birefringent Crystals in Cardiac and Prostatic Tissues, an Observational Study
<b>AUTHORS</b>	Park, Jane; Roudier, Martine; Soman, Divya; Mokadam, Nahush; Simkin, Peter

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Luca Mascitelli Comando Brigata alpina "Julia"/Multinational Land Force, Udine, ITALY
<b>REVIEW RETURNED</b>	16-Apr-2014

<b>GENERAL COMMENTS</b>	<p>Perhaps a journal better fitted to accept this paper would be a journal which deals with medical hypotheses</p> <p>The paper is interesting. However, the hypothesis of a pathophysiological role of hyperuricemic inflammation should be better stated.</p> <p>I would suggest to better highlight that gout, but not hyperuricemia, has been shown to represent a risk factor for all-cause and cardiovascular mortality. In this setting, it has been found that a plausible pathophysiologic mechanism might be related to inflammation, which represents the characteristic difference between gout and hyperuricemia. Indeed, it is well known that hyperuricemia and/or crystal deposition are not sufficient to cause gouty attacks. It has been proposed that iron may represent a factor which triggers inflammation and heightens inflammation, and in particular cardiovascular risk in gouty patients.</p> <p>Accumulating evidence suggests that gout is a disease of iron overload, and that uric acid accumulation, as both an antioxidant and an iron chelator, is in response to the iron overload.</p> <p>Authors should discuss this issue and perform a better definition of their hypothesis.</p> <p><b>SUGGESTED REFERENCES</b></p> <p>Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P. Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. <i>Biochem J</i> 1986;235:747-54.</p> <p>Ghio AJ, Ford ES, Kennedy TP, Hoidal JR. The association between serum ferritin and uric acid in humans. <i>Free Radic Res</i> 2005;39:337-42. [Erratum in: <i>Free Radic Res</i> 2007;41:1385].</p> <p>Mascitelli L, Pezzetta F, Goldstein MR. Comment on: Gout: an</p>
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	independent risk factor for all-cause and cardiovascular mortality. Rheumatology (Oxford). 2010 Jul;49(7):1421-2;
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<b>REVIEWER</b>	Hyon Choi Boston Univ, USA
<b>REVIEW RETURNED</b>	07-May-2014

<b>GENERAL COMMENTS</b>	<p>The authors describe interesting and intriguing findings that have a potential implication in the role of uric acid on the pathogenesis of CVD and prostatitis. While the lack of clinical correlation is a limitation, I agree with the authors' suggestion that the prevalences in these tissues are valuable in their own right, particularly for future larger-scale prospective studies.</p> <p>I have provided minor comments below for the authors' consideration.</p> <ol style="list-style-type: none"> <li>1. The introduction seems too long (~3.3 pages). I would consider moving some of its contents to the discussion.</li> <li>2. Having said that, the discussion is not short either, including a mini-case description, which I find interesting as well. Thus, I would consider solidifying some overlapping concepts between the intro and discussion.</li> <li>3. It would be helpful if you could expand a little on the limitations of conventional staining methods for identifying urate/uric acid crystals (or other pathologic crystals, if any). Also, please consider expanding a little on the crystal morphology differences between urate vs. uric acid crystals that the authors have referred to.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Regarding Reviewer 1's comments about iron, we have added a brief discussion of urate as a chelator of metal ions in the revised manuscript.

Regarding Reviewer 2's comments, the introduction and discussion may seem lengthy, but we anticipate some readers from other fields will be interested in only one of the three tissues surveyed. Given the disparate nature of the tissues, background and explanation of their relationships to uric acid was necessary. We have also addressed his points about staining and uric acid crystal morphology within the text of the manuscript.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Hyon Choi Boston Univ. USA
<b>REVIEW RETURNED</b>	17-Jun-2014

<b>GENERAL COMMENTS</b>	The authors have responded to my comments nicely.
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